Original Article

Vulvovaginal Candidiasis During Pregnancy: An Integrated Analysis of Hormonal and Immunological Interplay

Hormonal and Immunological Interplay in VVC

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ABSTRACT

Objective: To investigate the combined immunological and hormonal alterations associated with pregnancy-associated vulvovaginal candidiasis (VVC).

Study Design: A case control study

Place and Duration of Study: This study was conducted at the College of Health and Medical Technology, Middle Technical University, from April to September 2025.

Methods: From each participant, blood and vaginal swab samples were collected prior analysis, involving 90 pregnant women, including 47 patients diagnosed with VVC and 43 healthy controls. Sabouraud dextrose agar (SDA) and CHROMagar *Candida* media were used for fungal cultivation for the detection of Candida. Enzyme-linked immunosorbent assay (ELISA) was used to evaluate serum levels of estradiol, progesterone, IL-10, and cortisol.

Results: The findings showed that significant differences were observed between patients and controls ($p < 0.001$), with patients showing considerably higher levels of cortisol and IL-10 along with reduced levels of progesterone and estradiol.

Conclusion: Overall, the current study suggests that VVC in pregnant women is associated with hormonal disturbance, immunological dysregulation, and neuroendocrine alteration. This study highlights the combined role of immunological and hormonal factors in the pathogenesis of VVC.

Key Words: Vulvovaginal candidiasis, Pregnancy, IL-10, Immune dysregulation, Cortisol, Estrogen

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INTRODUCTION

Vulvovaginal candidiasis (VVC) is considered one of the widely frequent fungal infections that affect women in their reproductive years[1] . *Candida* albicans is an opportunistic commensal microorganism that infect the vaginal microbiome and may associate to the development of vaginal infection[2]. Pregnancy is one of several factors that contribute to increased susceptibility to Vulvovaginal candidiasis due to hormonal and immunological alteration[3]. Studies suggest that estrogen may elevate glycogen storage within vaginal epithelial cell**.** which may create a nutrient-rich environment that could encourage colonization and pathogenicity of *Candida* infection[4]. Additionally, progesterone may have an impact on immunological responses and epithelial integrity, even though, compared to estrogen, its role is limited and poorly understood[5]. In addition, Interleukin-10 (IL-10), one of the primary cytokines that is particularly significant because of its anti-inflammatory effects and function in maintaining immunological homeostasis[6]. Notably, Cortisol is a significant stress hormone with immunosuppressive properties, has been linked to an increased risk of genitourinary infections and alteration of vaginal immunological homeostasis. Elevated cortisol levels during pregnancy could weaken host defenses and worsen vaginal dysbiosis, which would promote opportunistic infections like *Candida*[7]. Limited studies have investigated the combined hormonal and immunological alterations associated with pregnancy-related VVC, highlighting an important gap in current knowledge. Therefore, this study aimed to evaluate serum estradiol, progesterone, IL-10, and cortisol levels in pregnant women with VVC and healthy controls.

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METHODS

The present study was performed in the obstetrics and gynecology and microbiological laboratory department

of Baghdad Teaching Hospital in Baghdad, Iraq, during the period from March to August 2025. Among the 90 pregnant women aged between 16 and 45 years were participated in the research, there were 47 cases and 43 controls. During morning visits, blood and vaginal swab samples were collected. Each patient underwent a speculum examination by a gynecologist who documented clinical signs and symptoms. Demographic informations of all participants was recorded, including, age, gestational age, number of pregnancies, history of abortions, and chronic disease.

Inclusion and exclusion criteria: Pregnant women with vaginal candidiasis and healthy controls were included, while those with immune disorders, prior antimicrobial treatment, vaginal bleeding or other vaginal infections were excluded.

Ethical Approval: The ethical approving was obtained from the Medical Ethics Committee of Middle Technical University (MEC: 72; 11 January 2025). All procedures followed the Declaration of Helsinki, and all participants provided written informed consent. All participants took part voluntarily, and all data were anonymized and kept confidential.

Laboratory analysis: Venous blood samples were obtained from the patient and control groups using standardized protocols. Estradiol (E2), progesterone, cortisol, and interleukin-10 (IL-10) Levels were assessed using the enzyme-linked immunosorbent assay (ELISA) as it provides a sensitive and quantitative method for measuring hormonal and cytokine concentration[8]. Following the manufacturer-provided instructions ELK Biotechnology **(**China), ELISA absorbance was determined using HumaReader HS microplate reader (Germany). In addition, vaginal swabs were aseptically collected by a qualified gynecologist using sterile techniques, using sterile cotton swabs for the isolation of *Candida* species. The samples were later inoculated into Sabouraud dextrose agar (SDA) and CHROMagar (India), media for fungal detection. The inoculated plates were incubated at 37°C for 24–48 hours. Subsequently, the resulting colonies were examined microscopically to confirm the characteristic morphology of *Candida* species.

Statistical Analysis: SPSS version 26 was used to statistically analyze all of the data. For categorical parameters, the chi-square (χ^2) test was performed, and group means were compared using independent samples t-tests. Sensitivity, specificity, and ideal cut-off values were examined using ROC curve analysis. A p-value below 0.05 was considered statistically significant, while a p-value below 0.01 was considered highly significant..

RESULTS

Demographic characteristics: Table 1 represents the demographic and clinical characteristics of the study groups, it shows no significant differences between the negative and positive groups in age ($p = 0.136$), trimester ($p = 0.75$), number of previous pregnancies ($p = 0.726$), history of abortion ($p = 0.372$), or chronic diseases ($p = 1.000$), indicating that the groups were comparable.

Estimation of Biomarkers: Biomarker levels are represented in Table 2. Including the mean and standard deviation of immunological and hormonal biomarkers between patients and controls. The results showed significant differences between patients and controls ($p < 0.001$). Patients exhibited lower levels of estradiol (337.99 ± 59.67 vs 736.79 ± 192.81), and progesterone (8.85 ± 2.39 vs 20.13 ± 7.08), along with higher levels of IL-10 (126.66 ± 18.62 vs 62.20 ± 14.97), and cortisol (41.95 ± 13.81 vs 22.81 ± 5.37).

Table No. 1. Demographic characteristics among patients and control.

Parameter		**Patient** N. (%)	**Control** N. (%)	**Total**	**p-value**
Age group	18-25	18 (38.3)	12 (27.9)	30 (33.3)	0.136 (NS)
	26-35	27 (57.4)	24 (55.8)	51 (56.7)	
	36-45	2 (4.3)	7 (16.3)	9 (10)	
Trimesters	First	2 (4.3)	0 (0)	2 (2.2)	0.208 (NS)
	Second	3 (6.4)	6 (14)	9 (10)	
	Third	42 (89.4)	37 (86)	79 (87.8)	
Previous Pregnancies	1-2	16 (34)	18 (41.9)	34 (37.8)	0.726 (NS)
	3-4	22 (46.8)	17 (39.5)	39 (43.3)	
	>5	9 (19.1)	8 (18.6)	17 (18.9)	
Previous abortion		18 (38.3)	12 (27.9)	30 (33.3)	0.296 (NS)
Chronic disease		13 (27.7)	11 (25.6)	24 (26.7)	0.824 (NS)

Data are shown as number (percentage). Group differences were analyzed using the chi-square (χ^2) test. NS, not significant.

Receiver operating characteristic (ROC) analysis: ROC analysis demonstrated a high discriminative ability of IL-10 (AUC = 1.000). With an ideal cutoff value of 72.85 pg/mL achieving 100% sensitivity and specificity. However, this result should be viewed with caution given the relatively small number of participants and lack of external validation. Cortisol also showed moderate to high discriminative

performance (AUC = 0.910), with a cutoff value of 22.5 ng/mL yielding 95.7% sensitivity and 65.1% specificity. In contrast, estradiol and progesterone exhibited inverse diagnostic patterns, with lower levels associated with the positive group ($p < 0.001$ for all biomarkers), as shown in Figure No. 1.

Table No. 2. determination of biomarker levels of the study groups

biomarker	Mean ± SD		p-value
	patient	control	
Estradiol (E2) (pg/ml)	337.99 ± 59.67	736.79 ± 192.81	p < 0.001
Progesterone (ng/ml)	8.85 ± 2.39	20.13 ± 7.08	p < 0.001
IL-10 (pg/ml)	126.66 ± 18.62	62.20 ± 14.97	p < 0.001
Cortisol (ng/ml)	41.95 ± 13.81	22.81 ± 5.37	p < 0.001

Values are reported as mean ± standard deviation (SD). IL-10 stands for interleukin-10. A p-value below 0.05 was considered significant.

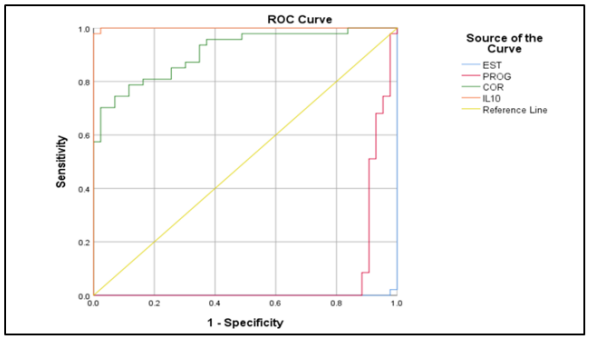

Figure No. 1: (ROC) analysis of Estrogen, Progesterone, IL-10, and Cortisol among Patients and Controls.

DISCUSSION

The present study provides new insights through a combined evaluation of immunological and hormonal alterations in pregnancy-associated vulvovaginal candidiasis, this multifactorial approach has been insufficiently addressed in previous studies, which have largely focused on individual factors. Our study demonstrated substantial differences in immunological and hormonal parameters within pregnant women with vulvovaginal candidiasis, it showed a significant increase in IL-10 levels and cortisol as well as decreased estradiol and progesterone. The two groups were similar in their demographic characteristics, indicating a fair baseline comparability, supporting that the observed alterations in IL-10, cortisol, estradiol, and progesterone are likely due to disease-related mechanisms rather than confounding elements. According to some studies that are in line with our findings, showed no statistically meaningful differences in some demographic and clinical factors between groups, indicating that disease occurrence may be more strongly associated with biological and immunological regulations rather than baseline characteristics[9]. Notably, Pregnancy-related changes may enhance immune tolerance, making an optimal condition for the growth and persistence of *Candida* species[10,11]. The present study found that pregnant women with vulvovaginal candidiasis exhibited significantly lower blood levels of estradiol (E2) and progesterone compared to healthy controls. Studies indicated that estrogen may promote *Candida* growth by increasing glycogen availability and modifying local immune responses, which would facilitate fungal persistence.[12]. Consequently, these findings are in line with previous reports revealed that women with recurrent vulvovaginal candidiasis had significantly lower serum progesterone levels than healthy controls. This suggests that hormonal alterations could possibly affect the pathogenesis of VVC[13]. According to experimental models, progesterone had no apparent effect on the susceptibility to vaginal *Candida* infection, whereas estrogen was the main hormone that contributed to persistent infection[14]. Notably, limited studies have directly measured blood progesterone levels in patients with VVC. Numerous factors might account for the differences between our results and previous studies. First of all, pregnancy is characterized by notable immunological and endocrine changes were the subject of the current study. Furthermore, determination of systemic hormone levels could not accurately represent local vaginal hormonal activity and concentrations[15]. The majority of studies have examined hormonal levels in the vaginal fluid, interestingly, the elevated cortisol levels observed in the present study may contribute to reduced gonadotropin secretion, that could influence estrogen and progesterone production[16]. According to reports elevating cortisol during chronic stress can decrease estrogen production[17]. This may represent another reason why estrogen levels have been decreased in the current study. Also, Inflammatory reactions linked to infections could lower hormone levels by changing endocrine regulations[18]. Our results may also be affected by differences in sample size, gestational age, laboratory measurement methods, and demographics. Our study revealed that IL-10 levels were markedly increased in women with VVC. These findings are in line with previous studies that suggest women with VVC have elevated IL-10 levels. Studies indicated that IL-10 levels are increased in recurrent vulvovaginal candidiasis. As experimental studies reported, higher IL-10 expression during recurrent *Candida* infection may promote fungal persistence and reduction in fungal clearance[19]. Therefore, these findings are consistent with the idea that, increased IL-

10 levels in VVC may reflect immunological imbalance, although IL-10 also has protective anti-inflammatory roles. The significant elevation of IL-10 observed suggests a shift toward an anti-inflammatory immune dysregulation that could restrict effective antifungal defense. Although, IL-10 plays a protective function in reducing tissue damage. Women with VVC in the current study had considerably higher serum cortisol levels than controls. A clinical study indicates that Women with VVC had considerably lower early-morning cortisol levels, which may indicate long-term stress**,** that could compromise immunological control and increase the persistence of the disease[20]. Stress-induced cortisol release may be associated with alterations in vaginal microbial balance, weaken estrogen-dependent vaginal immunity thus increases the risk of vulvovaginal infection[21]. The elevated cortisol levels observed in the present study are inconsistent with some previous studies. This lack of agreement may be partly explained by differences in sample type, as serum and salivary cortisol levels may differ significantly, particularly under pathological conditions. In this context, serum cortisol represents total hormone levels in circulation, whereas salivary cortisol reflects the unbound, biologically active fraction, which can provide a more functionally relevant measure in clinical and research settings[22]. Based on ROC analysis, IL-10 showed particularly high accuracy, whereas cortisol exhibited high sensitivity with moderate specificity, indicating that susceptibility to VVC is not determined by a single element, but complex interactions between host immunity and endocrine interactions. Our findings should be interpreted in light of several limitations, including the relatively small sample size and the fact that the study was conducted at a single center, and the use of serum rather than local vaginal measurements. In addition, the study's cross-sectional design limits causal interpretation.

CONCLUSION

Vulvovaginal candidiasis (VVC) during pregnancy is influenced by several factors including immunological and hormonal dysregulation. Women who were infected showed low levels of estradiol and progesterone, along with significantly elevated levels of IL-10 and cortisol when compared to healthy controls, as a result, these findings may indicate a disturbance in the immuno-endocrine balance. The present findings support the concept that VVC is predominantly an immunopathological condition influenced by host immune regulation and the hormonal environment. Moreover, IL-10 and cortisol may also have potential diagnostic value. Overall, the present investigation suggests a potential interaction between hormonal and immunological factors in pregnancy-associated VVC and may provide more development of diagnostic and therapeutic strategies.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Ali Fayez Noor, Abdulameer Jasim Mohammed
Drafting or Revising Critically:	Ali Fayez Noor, Omar Sadik Shalal
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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